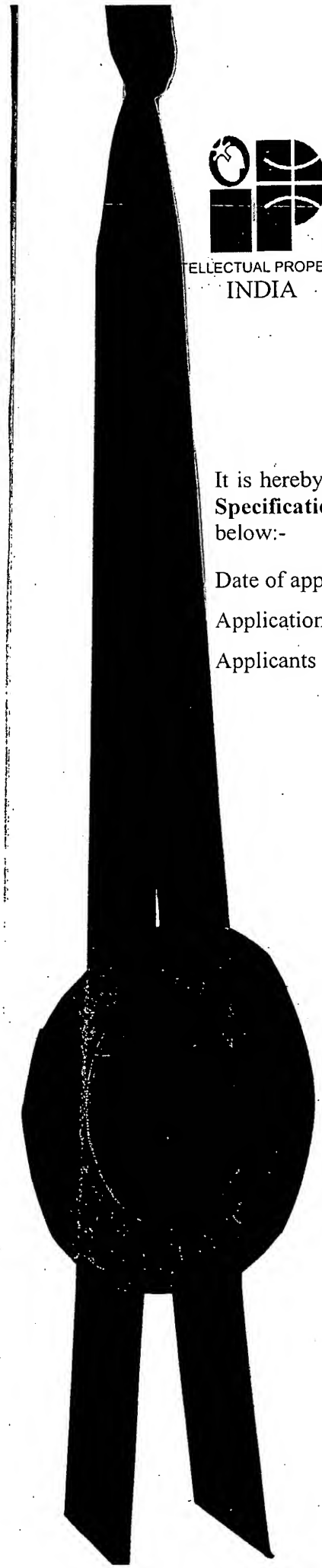

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INDIA

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CERTIFIED COPY OF
PRIORITY DOCUMENT

GOVERNMENT OF INDIA
PATENT OFFICE
Ministry of Commerce and Industry
Department of Industrial Policy and Promotion

It is hereby certified that annexed here to is a true copy of **Application, Complete Specification, Abstract & Drawing** of the patent application as filed and detailed below:-

Date of application : **12-08-2002**

Application No : **594/MAS/2002**

Applicants : **M/s. Dr. Reddy's Laboratories Limited,**
An Indian Company having its registered office at
7-1-27, Ameerpet, Hyderabad – 500 016,
A.P., India.

In witness there of
I have here unto set my hand

Dated this the 31st day of March 2005
10th day of Chaitra, 1926(Saka)

By Authority of
THE CONTROLLER GENERAL OF PATENTS,
DESIGNS AND TRADE MARKS.

(M.S.VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE BRANCH
Guna Complex, 6th Floor, Annex.II
No.443, Anna Salai, Teynampet,
Chennai – 600 018. India.

Received Rs5000 in Cash
Cheque/M.O./P.O./D.D/on 12/08
Vide C.B.R. No. 44460 02

FORM 1

THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7and Rule 33A)

We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare

1. (a) that we are in possession of an invention titled "**Novel amorphous form of 3-[2-(Dimethylamino) ethyl]-N-methyl-1H-indole-5-methane sulfonamide succinate (Sumatriptan succinate).**

(b) that the complete specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

2. further declare that the inventors for the said invention are **Satyanarayana Reddy Manne, Thirumalai Rajan Srinivasan, Suryanarayana Murthy Mokkarala Kodanda Ram Prasad Achampeta and Mallepally Srinivas Reddy.** All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad – 500 016, Andhra Pradesh.**

3. that we are the assignee of the true and first inventors

4. that our address for service in India is as follows;

Dr. Manne Satyanarayana Reddy,
Vice President-R&D
Dr. Reddy's Laboratories Limited
7-1-27, Ameerpet
Hyderabad, A.P., 500 016

5. following declaration was given by inventors.
We, the true and first inventors for this invention declare that the applicant herein is our assignee.

Signed)_____
Manne Satyanarayana Reddy,
H.No. 8-3-167/D/16,
Kalyan Nagar,
Near AG Colony,
Erragadda,
Hyderabad-500 038.

Signed)_____
Srinivasan Thirumalai Rajan,
Plot No. 12,
Lake view Enclave,
Miyapur,
Hyderabad-500 050.

Signed)_____

Mokkarala Suryanarayana Murthy,
Flat No. 301,
Kranthi Classic Apartments,
Prashanthinagar colony,
A.S. Rao Nagar,
Hyderabad – 500 062.

Signed)_____

Achampeta Kodanda Ram Prasad,
H.No.LIG-91,
Phase-I,
Dharma Reddy Colony,
KPHB, Kukatpally,
Hyderabad – 500 072.

Signed)_____

Mallepally Srinivas Reddy,
H.No.22-10,
Vivekananda nagar,
Dilsukhnagar,
Hyderabad – 500 060.

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application
7. following are the attachments with the application
   (a) complete specification (---11- pages, in triplicate)
   (b) abstract of the invention (--01- page, in triplicate)
   (c) drawings (---01- pages, in triplicate)
   (d) fee Rs. 5000.00 (five thousand rupees only) in A/C Payee Cheque vide No. 336257, dated 17.07.2002 drawn on HDFC Bank Limited, Lakdikapool, Hyderabad.

We request that a patent may be granted to us for the said invention

Dated this 08th day of ~~July~~ August 2002.

To
The Controller of Patents
The Patent Office, Chennai.

(Signed)_____

Dr. Manne Satyanarayana Reddy,
Vice President-R&D
Dr. Reddy's Laboratories Limited.

FORM-2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION
(SECTION 10)

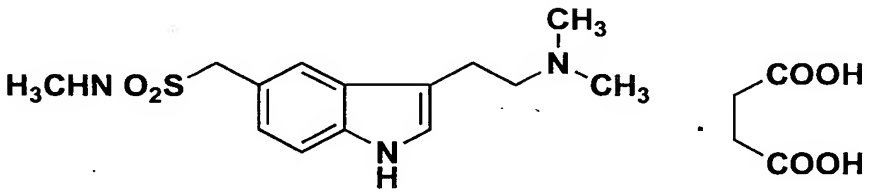
Novel Amorphous Form of 3-[2-(Dimethylamino) ethyl]-N-Methyl-1H-Indole-5-methane Sulfonamide succinate (Sumatriptan succinate)

Dr. Reddy's Laboratories Limited,
An Indian Company having its registered office at
7-1-27, Ameerpet,
Hyderabad - 500 016, A.P., India

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed.

FIELD OF THE INVENTION:

The present invention relates to the novel amorphous form of 3-[2-(dimethylamino) ethyl]-N-methyl-1H-indole-5-methane sulfonamide succinate. It also relates to the process for the preparation of novel amorphous form of 3-[2-(dimethylamino) ethyl]-N-methyl-1H-indole-5-methane sulfonamide succinate. It is generically known as Sumatriptan succinate, marketed under the name "Imitrex", which can be depicted as Formula (1).



Formula (I)

Sumatriptan is an anti migraine compound, efficacious in the treatment of migraine. It has no significant effect on blood pressure, heart rate and no significant bronco constrictor effect on the lungs.

BACKGROUND OF THE INVENTION:

USP 4,816,470 claimed Sumatriptan and related compounds generically. It also claimed the pharmaceutical composition and method of treatment using Sumatriptan related compounds.

The '470 patent relates to substituted Indole derivatives, methods of making and using them. The patent discloses a process for the preparation of analogs of Sumatriptan and its related compounds, their salts. The process for the preparation of monomethyl analog of Sumatriptan comprises of refluxing the mixture of 4-[2-(4-

Chlorobutylidene) hydrazino]-N-methyl-benzene methanesulponamide in chloroform and polyphosphate ester in chloroform and on further reaction workup resulted 3-(2-chloroethyl)-N-methyl-1H-indole-5-mehanesulphonamide. This on further heating with ethanolic solution of methylamine and followed by reaction workup resulted the monomethyl analog of Sumatriptan.

USP 5,037,845 claimed Sumatriptan and Sumatriptan succinate specifically along with pharmaceutical composition and method of treatment using Sumatriptan.

The Patent also disclosed the process for the preparation of Sumatriptan, its related compounds and their salts.

Our co-pending Indian Patent application vide No.451/MAS/2002 disclosed the novel crystalline forms of Sumatriptan succinate, which are designated as Form-I and Form-II along with their process for preparation.

Another co-pending Indian Patent application vide No.452/MAS/2002 described the purification process for obtaining highly pure Sumatriptan.

Many of the patents were disclosed the process for the preparation of Sumatriptan and its salts including succinate, but none of these patents were described the existence of an amorphous form of Sumatriptan succinate.

It has been disclosed earlier that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to crystalline forms. For some therapeutic indications one bioavailabilility pattern may be favored over another. An amorphous form of Cefuroxime axetil is a good example for exhibiting higher bioavailability than the crystalline form.

During our laboratory experimentation as a part of process development, novel

amorphous form of Sumatriptan succinate was resulted while crystallizing the Sumatriptan in different solvents.

Hence, the main aspect of the present invention is to provide the novel amorphous form of Sumatriptan succinate. The invention also provides the process for the preparation of novel amorphous form of Sumatriptan succinate.

The novel amorphous form of Sumatriptan succinate of the present invention is characterized by X-ray powder diffractogram, which is not having well-resolved peaks.

The novel amorphous form of Sumatriptan obtained in the present invention is free flowing, non-hydrated, non-solvated and thermally stable solid.

The process for the preparation of novel amorphous form of the present invention is simple, eco-friendly and easily scalable.

SUMMARY OF THE INVENTION:

The present invention relates to the novel amorphous form of Sumatriptan succinate.

The present invention also relates to process for the preparation of amorphous form of Sumatriptan succinate. The process for the preparation of novel amorphous form of Sumatriptan succinate comprises refluxing the aqueous mixture of Sumatriptan succinate salt in alcoholic solvents such as methanol or nitrile solvents such as acetonitrile followed by evaporation of the solvent from the filtrate. The resulting residue is triturated with water immiscible aromatic or aliphatic hydrocarbon solvents such as cyclohexane to afford the amorphous form of Sumatriptan succinate.

The present invention also relates to provide a process for the preparation of an amorphous form of Sumatriptan succinate from Sumatriptan using succinicacid and following the similar process as mentioned above.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS:

Fig-1 is a characteristic X-ray powder diffraction pattern of the present invention.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention relates to the novel amorphous form of Sumatriptan succinate and a process for the preparation thereof.

The present invention of novel amorphous form of Sumatriptan succinate is characterized by X-ray powder diffractogram. The X-ray powder diffraction pattern of novel amorphous form of Sumatriptan succinate is measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The novel amorphous form of Sumatriptan succinate of the present invention is having the X-ray powder diffractogram pattern is substantially as depicted in Figure (1).

Another embodiment of the present invention is to provide the process for the preparation of novel amorphous form of 3-[2-(Dimethylamino) ethyl]-N-Methyl-1H-indole-5-methane sulfonamide succinate (Sumatriptan succinate), which comprises,

a) refluxing the aqueous mixture of Sumatriptan or its succinate salt in C_1-C_5 straight or branched chain alcoholic solvents comprising of methanol, ethanol, n-propanol, isopropanol, n-butanol, 2- butanol, n-pentanol and 2-pentanol, preferably methanol **OR** in nitrile solvents comprising of acetonitrile and propionitrile, preferably acetonitrile;

b) adding the succinic acid in case of Sumatriptan as a starting material in step (a);

c) filtering the reaction mixture obtained in either step (a) or step (b);

d) distilling off the solvent from the filtrate obtained in step (c);

e) adding water immiscible aliphatic or alicyclic hydrocarbon solvents comprising of petroleum ether, hexane, cyclohexane or heptane, preferably cyclohexane to the residue obtained in step (d);

f) stirring the mass obtained in step (e) till the material separation completes;

g) filtering the solid obtained in step (f) by conventional methods;

h) drying the compound obtained in step (g) at a temperature of 30-50^{O}C, preferably 25-35^{O}C under vacuum to afford the required novel amorphous form of Sumatriptan succinate.

The crystalline Form-I or Form-II of sumatriptan succinate can also be used in the above process to prepare novel amorphous form.

The present inventive substance is non-hydrated, non-solvated, free flowing and thermally stable solid; hence it is well suited for pharmaceutical formulations.

Hence, the present invention is directed to provide novel amorphous form of Sumatriptan succinate.

The process for the preparation of present invention is simple, eco-friendly and commercially viable.

It is noteworthy to mention that the process for the preparation of Sumatriptan or its pharmaceutical acceptable salts including succinate was disclosed in prior art references known in the art. Sumatriptan succinate can also be outsourced.

The process for the preparation of crystalline Form-I and Form-II of Sumatriptan succinate was disclosed in our co-pending Indian patent application number vide No.451/MAS/2002.

Purification process for obtaining highly pure Sumatriptan was disclosed in our

another co-pending Indian Patent application vide No.452/MAS/2002.

The present invention is illustrated by the following examples, which are not intended to limit the effective scope of the claims.

Preparation of the novel amorphous form of Sumatriptan succinate:

Example 1:

Crystalline Form-I of Sumatriptan succinate (15.0 grams), water (75.0 ml) and methanol (150.0 ml) were heated to reflux temperature. The reaction mass was stirred for 15-30 minutes at reflux and filtered in hot condition. The solvent was distilled off completely from the filtrate under reduced pressure at a temperature of below 35-45 ° C. Cyclohexane (100 ml) was added to the resulting residual mass and stirred for 1-2 hours at a temperature of 25-35^{O}C to crystallize the solid. Then the solid was filtered, washed with cyclohexane (50 ml) and on subsequent drying under vacuum at a temperature of 25-35^{O}C resulted the novel amorphous form of Sumatriptan succinate.

(Weight: 12.5 grams, MC 0.5% w/w)

Example-2:

Crystalline Form-I of Sumatriptan succinate (15.0 grams), water (75.0 ml) and Acetonitrile (150.0 ml) were heated to reflux temperature. The reaction mass was stirred for 15-30 minutes at reflux and filtered in hot condition. The solvent was distilled off completely from the filtrate under reduced pressure at a temperature of below 35-45 ° C. Cyclohexane (100 ml) was added to the resulting residual mass and stirred for 1-2 hours at a temperature of 25-35^{O}C to crystallize the solid. Then the solid was filtered, washed with cyclohexane (50 ml) and on subsequent drying under

vacuum at a temperature of 25-35^{O}C resulted the novel amorphous form of Sumatriptan succinate.

(Weight: 13.0 grams, MC 0.5% w/w)

Example-3:

Crystalline Form-II of Sumatriptan succinate (10.0 grams), water (50.0 ml) and methanol (100.0 ml) were heated to reflux temperature. The reaction mass was stirred for 15-30 minutes at reflux and filtered in hot condition. The solvent was distilled off completely from the filtrate under reduced pressure at a temperature of below 35-45 ° C. Cyclohexane (100 ml) was added to the resulting residual mass and stirred for 1-2 hours at a temperature of 25-35^{O}C to crystallize the solid. Then the solid was filtered, washed with cyclohexane (50 ml) and on subsequent drying under vacuum at a temperature of 25-35^{O}C resulted the novel amorphous form of Sumatriptan succinate.

(Weight: 9.3 grams, MC 0.6% w/w)

Example-4:

Crystalline Form-II of Sumatriptan succinate (10.0 grams), water (50.0 ml) and acetonitrile (100.0 ml) were heated to reflux temperature. The reaction mass was stirred for 15-30 minutes at reflux and filtered in hot condition. The solvent was distilled off completely from the filtrate under reduced pressure at a temperature of below 35-45 ° C. Cyclohexane (100 ml) was added to the resulting residual mass and stirred for 1-2 hours at a temperature of 25-35^{O}C to crystallize the solid. Then the solid was filtered, washed with cyclohexane (50 ml) and on subsequent drying under

vacuum at a temperature of 25-35^{O}C resulted the novel amorphous form of Sumatriptan succinate.

(Weight: 9.5 grams, MC 0.8% w/w)

Example-5:

Sumatriptan (10.0 grams), water (50.0 ml), succinic acid (3.99 grams) and acetonitrile (100.0 ml) were heated to reflux temperature. The reaction mass was stirred for 15-30 minutes at reflux and filtered in hot condition. The solvent was distilled off completely from the filtrate under reduced pressure at a temperature of below 35-45^{O}C. Cyclohexane (100 ml) was added to the resulting residual mass and stirred for 1-2 hours at a temperature of 25-35^{O}C to crystallize the solid. Then the solid was filtered, washed with cyclohexane (50 ml) and on subsequent drying under vacuum at a temperature of 25-35^{O}C resulted the novel amorphous form of Sumatriptan succinate.

(Weight: 12.0 grams, MC 0.7% w/w)

The Sumatriptan succinate obtained from the above examples are having similar XRD pattern, which shows a plain halo with no peaks indicating the amorphous nature.

DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWING

Fig.1 is characteristic X-ray powder diffraction pattern of novel amorphous form of Sumatriptan succinate

Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

It shows a plain halo with no peaks, which is characteristic of the amorphous nature of product.

We claim:

1. A novel amorphous form of 3-[2-(dimethylamino) ethyl]-N-methyl-1H-Indole-5-methane sulfonamide succinate (Sumatriptan succinate).
2. The novel amorphous form of Sumatriptan succinate of claim 1, which is characterized by Powder X-ray diffractogram.
3. The amorphous form of Sumatriptan succinate according to claims 1 and 2, which provides X-ray powder diffraction pattern substantially in accordance with Figure (1).
4. A process for the preparation of novel amorphous form of 3-[2-(dimethylamino) ethyl]-N-Methyl-1H-Indole-5-methane sulfonamide succinate (Sumatriptan succinate), which comprises:
   a) refluxing the aqueous mixture of Sumatriptan or its succinate salt in C_1-C_5 straight or branched chain alcoholic solvents comprising of methanol, ethanol, n-propanol, isopropanol, n-butanol, 2- butanol, n-pentanol and 2-pentanol, preferably methanol **OR** in nitrile solvents comprising of acetonitrile and propionitrile, preferably acetonitrile;
   b) adding the succinic acid in case of Sumatriptan as a starting material in step (a);
   c) filtering the reaction mixture obtained in either step (a) or step (b);
   d) distilling off the solvent from the filtrate obtained in step (c);
   e) adding water immiscible aliphatic or alicyclic hydrocarbon solvents comprising of petroleum ether, hexane, cyclohexane or heptane, preferably cyclohexane to the residue obtained in step (d);
   f) stirring the mass obtained in step (e) till the material separation completes;

g) filtering the crystallized solid obtained in step (f) by conventional methods;

h) drying the compound obtained in step (g) at a temperature of 30-50^{O}C, preferably 25-35^{O}C under vacuum to afford the required novel amorphous form of Sumatriptan succinate.

5. The process according to step (a) of claim 4, where in the sumatriptan succinate is crystalline Form-I.

6. The process according to step (a) of claim 4, where in the sumatriptan succinate is crystalline Form-II.

7. The process according to step (a) of claim 4, wherein the said alcoholic solvent is methanol.

8. The process according to step (a) of claim 4, wherein the said nitrile solvent is acetonitrile.

9. The process according to step (e) of claim 4, wherein the said alicyclic hydrocarbon solvent is cyclohexane

10. The process for the preparation of novel amorphous form of Sumatriptan succinate is substantially as here in described and exemplified.

Dated this 08th day of August 2002

Signed)_____
Dr. Manne Satyanarayana Reddy,
Vice President-R&D
Dr.Reddy's Laboratories Limited.

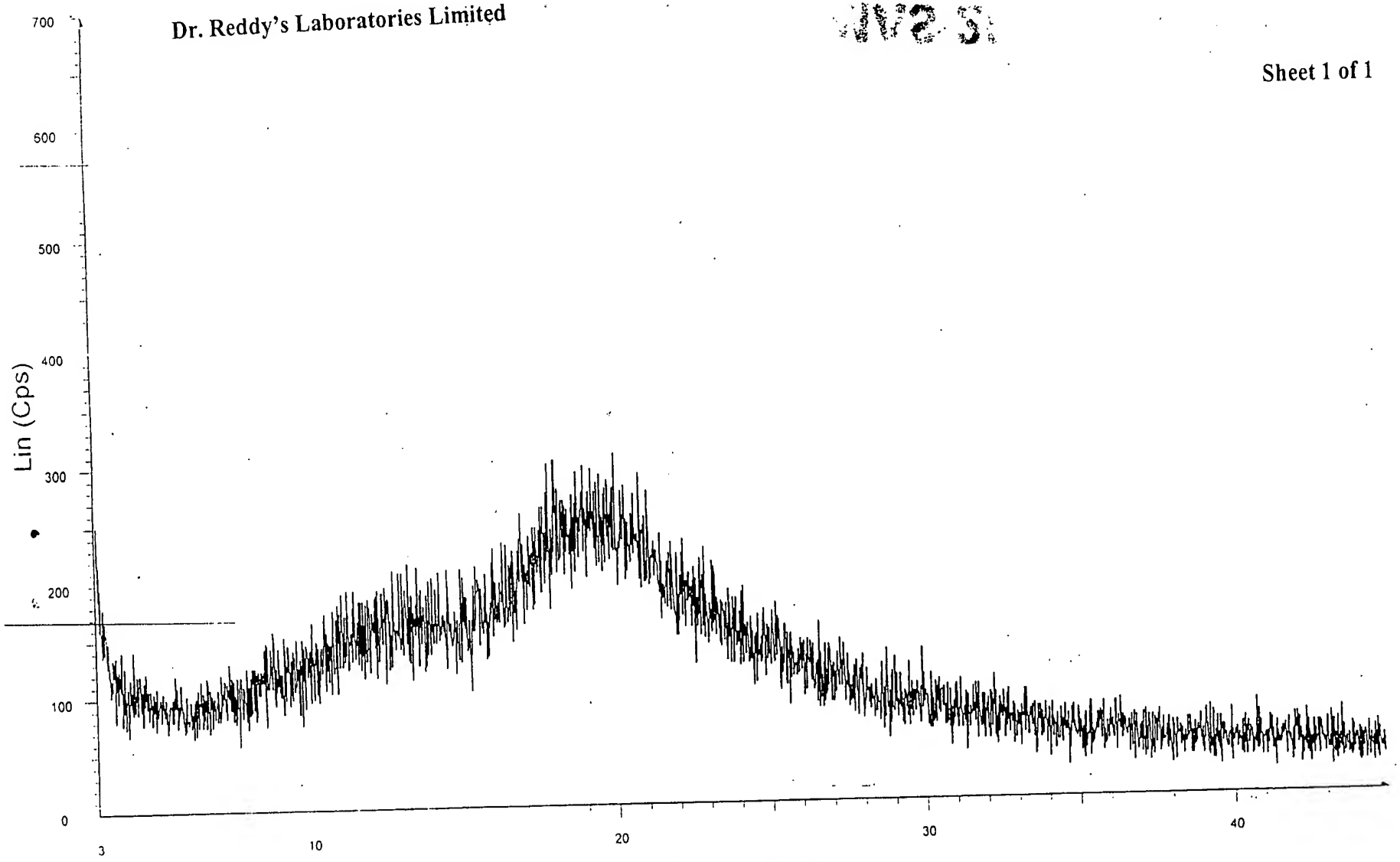
ABSTRACT

Title of the Invention: Novel Amorphous Form of 3-[2-(Dimethylamino) ethyl]-N-Methyl-1H-Indole-5-methane Sulfonamide succinate (Sumatriptan succinate)

The present invention relates to the novel amorphous form of Sumatriptan succinate of Formula (1). The present invention also relates to process for the preparation of amorphous form of Sumatriptan succinate. The process for the preparation of novel amorphous form of Sumatriptan succinate comprises refluxing the aqueous mixture of Sumatriptan or its succinate salt in alcoholic solvents such as methanol or nitrile solvents such as acetonitrile followed by evaporation of the solvent from the filtrate. The resulting residue is triturated with water immiscible aromatic or aliphatic hydrocarbon solvents such as cyclohexane to afford the amorphous form of Sumatriptan succinate.

Dr. Reddy's Laboratories Limited

Sheet 1 of 1



MANNE SATYANARAYANA REDDY

Fig. 1